

ERCC1 and ERCC2 Polymorphisms Predict Clinical Outcomes of Oxaliplatin-Based Chemotherapies in Gastric and Colorectal Cancer: A Systemic Review and Meta-analysis

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Abstract

Purpose: Nucleotide excision repair (NER) modulates platinum-based chemotherapeutic efficacy by removing drug-produced DNA damage. To summarize published data on the association between polymorphisms of NER genes (*ERCC1* and *ERCC2*) and responses to oxaliplatin-based chemotherapies, we carried out a meta-analysis of gastric and colorectal cancer for commonly studied polymorphisms *ERCC1* rs11615C>T and *ERCC2* rs13181T>G.

Patients and Methods: In 17 previously published studies, 1,787 cancer patients were treated with the oxaliplatin-based regimen. Primary outcomes included therapeutic response (TR; i.e., complete response + partial response vs. stable disease + progressive disease), progression-free survival (PFS), and overall survival (OS). We calculated OR or HR with 95% CIs to estimate the risk or hazard.

Results: We found consistent and clinically substantial risk or hazard for TR, PFS, and OS in the oxaliplatin-treated gastric and colorectal cancer patients with an ethnic discrepancy. For *ERCC1* rs11615C>T, the T allele was associated with reduced response and poor PFS and OS in Asians (TR: OR = 0.53 and 95% CI = 0.35–0.81; PFS: HR = 1.69 and 95% CI = 1.05–2.70; and OS: HR = 2.03 and 95% CI = 1.60–2.59). For *ERCC2* rs13181T>G, the G allele was associated with reduced response and poor PFS and OS in Caucasians (TR: OR = 0.56 and 95% CI = 0.35–0.88; PFS: HR = 1.41 and 95% CI = 1.02–1.95; and OS: HR = 1.42 and 95% CI = 1.11–1.81).

Conclusions: NER *ERCC1* rs11615C>T and *ERCC2* rs13181T>G polymorphisms are useful prognostic factors in oxaliplatin-based treatment of gastric and colorectal cancer. Larger studies and further clinical trials are warranted to confirm these findings. *Clin Cancer Res*; 17(6); 1632–40. ©2011 AACR.

Introduction

Fluoropyrimidines are essential in the treatment of gastric and colorectal cancer in advanced stages and have shown survival benefit compared with the best supportive care (1, 2). Oxaliplatin is the new generation of platinum drugs that improve response rate and survival after adding to the

5-fluorouracil (5-Fu)/leucovorin (LV) regimen. Combination treatment with 5-Fu/LV plus oxaliplatin (FOLFOX) is now considered the standard treatment of gastric and colorectal cancer, with a response rate of more than 40% for the first-line treatment (3, 4). Despite the efficacy of combined chemotherapies, a large proportion of patients display varying levels of resistance, indicating that the therapeutic efficacy has a remarkable interindividual variability. Since DNA kinking is the major feature of platinum–DNA adducts that block DNA replication and lead to cancer cell death (5, 6), which is recognized and repaired by the nucleotide excision repair (NER) pathway, it is conceivable that the interindividual difference in the NER capacity may influence the efficacy of oxaliplatin-based chemotherapy and clinical outcomes of the treated cancer patients.

ERCC1 and *ERCC2* proteins are major components of the NER complex, acting as the rate-limiting enzymes in the NER pathway. Several common and putatively functional single nucleotide polymorphisms (SNPs) of *ERCC1* and *ERCC2* have been identified, of which *ERCC1* rs11615 and rs3212986 SNPs (C118T and C8092A) have some effects on *ERCC1* mRNA expression (7), whereas *ERCC2* rs1799793 and rs13181 SNPs [Asp312Asn (G>A) and Lys751Gln (T>G), respectively] SNPs are associated with

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Translational Relevance

Combination treatment with oxaliplatin and fluoropyrimidines is the standard treatment of gastric and colorectal cancer which improves patient response and overall survival. The nucleotide excision repair (NER) pathway is responsible for the removal of DNA adducts caused by oxaliplatin and thus may influence chemotherapeutic efficacy. Our meta-analysis provided evidence of an association between NER *ERCC1* rs11615C>T and *ERCC2* rs13181T>G single nucleotide polymorphisms and clinical outcomes in gastric and colorectal cancer patients, both Asians and Caucasians, receiving oxaliplatin-based chemotherapy. Our results suggest that it is feasible to use a pharmacogenomic approach to predict clinical outcomes of oxaliplatin-treated gastric and colorectal cancer patients.

suboptimal DNA repair capacity (8, 9). Previous studies have suggested that *ERCC1* is a promising predictive marker for response to the platinum-based chemotherapy because of its low expression associated with increased chemotherapeutic sensitivity (10). Therefore, these *ERCC1* and *ERCC2* SNPs may be useful prognostic markers for treatment with platinum agents.

Because published reports of an association between NER SNPs and clinical outcome of platinum-based chemotherapy from individual studies are not consistent, we conducted a systemic review and meta-analysis to assess the evidence of effects of *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs on the efficacy of oxaliplatin-based chemotherapy in gastric and colorectal cancer patients.

Patients and Methods

Study selection

We searched for relevant publications before June 1, 2010, in English literature by using electronic MEDLINE and EMBASE databases with the following terms: "ERCC1," "ERCC2 or XPD," or "ERCC," "gastric or stomach cancer," "colon or colorectal cancer," "polymorphism or variant," and "treatment or chemotherapy." References of the retrieved articles were further screened for earlier original studies. The inclusion criteria were as follows: advanced, recurrent, or metastatic gastric or colorectal cancer; treated purely by regimens of FOLFOX (oxaliplatin plus 5-Fu/leucovorin) or XELOX (oxaliplatin plus capecitabine, a drug which converts to 5-Fu *in vivo*), excluding neoadjuvant chemotherapy; cancer histologically or pathologically confirmed; East Asian (China, Korea, and Japan) or Caucasian (European descendants) ethnicities; and *ERCC1* rs11615C>T and or *ERCC2* rs13181T>G genotyped. The corresponding authors were contacted to obtain missing information, and some studies were excluded if critical missing information was not obtained by our repeated requests. Abstracts, unpublished reports, and articles with

sample size less than 45 or written in non-English language were also excluded.

Statistical methods

We estimated the OR for objective response versus no response after platinum-based chemotherapy [CR (complete response) + PR (partial response) vs. PD (progressive disease) + SD (stable disease)], using the WHO criteria, ref. 11, or RECIST (Response Evaluation Criteria in Solid Tumors) criteria, ref. 12]. Progression-free survival (PFS) and overall survival (OS) were evaluated by pooled Cox proportional HRs and 95% CIs by published methods (13), because a meta-analysis of summary results is statistically as efficient as a joint analysis of individual participant data (14). We assessed the between-study heterogeneity by the Cochran Q test with a significance level of $P < 0.05$. We carried out initial analyses with a fixed-effect model and confirmatory analyses with a random-effect model, if there was significant heterogeneity. We used inverted funnel plots and the Egger test to examine the effect of publication bias. We compared the difference in the effect estimates between subgroups as described previously (15). All P values were 2-sided, and all analyses were carried out using the Stata software (Stata Corporation) and Review Manager (v5.0).

Results

We identified 65 related publications by initial screening (as of June 1, 2010), of which 21 publications seemed to meet the inclusion criteria. We excluded 1 study, in which data were inestimable and authors were unreachable (16), 2 studies that used other chemotherapeutic agents (i.e., irinotecan and cetuximab) in addition to FOLFOX or XELOX (17, 18), and 1 study with study sample size less than 45 (ref. 19; Fig. 1). As a result, the final data pool consisted of 17 studies, including 1,787 cancer patients (Table 1).

ERCC1 rs11615C>T

Objective response. Nine studies including 855 patients were eligible for the final analysis. In the dominant model, the minor variant T allele was not associated with objective response in all patients (T/T + C/T vs. C/C: OR = 0.89; 95% CI = 0.50–1.57; Fig. 2A) and no single study altered the result substantially by the sensitivity test. However, stratified analysis by ethnicity showed a significant difference in the estimates of effect between Asians and Caucasians ($P = 0.002$) and the T allele was associated with a significantly lower objective response rate in Asians (OR = 0.53; 95% CI = 0.35–0.81). When only colorectal cancer was included, the OR was similar to that of the overall patients (OR = 0.88; 95% CI = 0.42–1.87; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Progression-free survival. Eleven studies including 1,230 patients were eligible for the final analysis. The T allele was associated with a nonsignificant increase of hazard for PFS in all patients (T/T + C/T vs. C/C: HR =

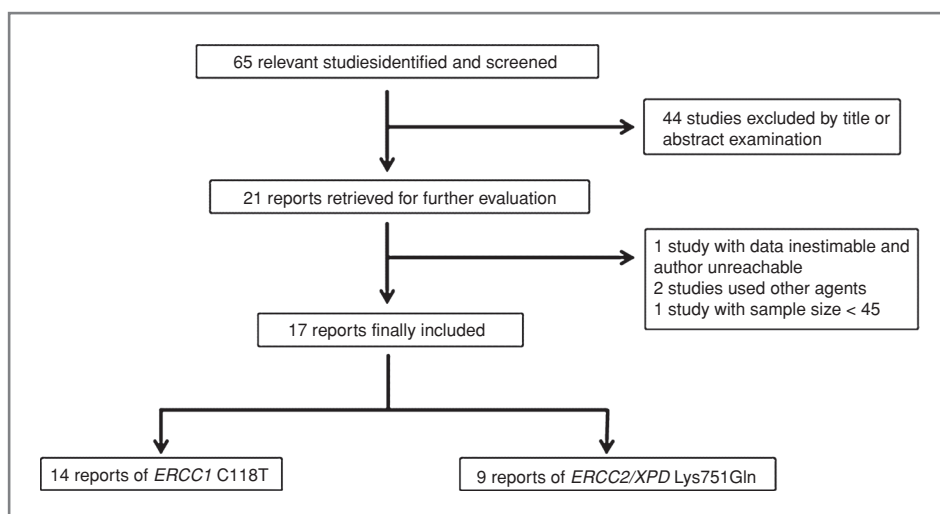


Figure 1. Study flow chart for the process of selecting the eligible publications.

Table 1. Studies on oxaliplatin-based chemotherapy and *ERCC1* (rs11615C>T) and *ERCC2* (rs13181T>G) polymorphisms included in the meta-analysis

Study	Country	Tumor	Drug	<i>n</i>	Biomarkers	SNPs	Allele frequency ^a
Asians							
Chang et al. (21)	Taiwan	Colorectal	FOLFOX	168	TR, OS, PFS	rs11615	T: 0.254
Lai et al. (34)	Taiwan	Colorectal	FOLFOX	188	TR, OS, PFS	rs13181	G: 0.080
Keam et al. (22)	Korea	Gastric	FOLFOX	73	TR, OS, PFS	rs11615	T: 0.260
						rs13181	G: 0.082
Liang et al. (35)	China	Colorectal	FOLFOX or XELOX	99	TR, PFS	rs11615	T: 0.288
Seo et al. (36)	Korea	Gastric	FOLFOX	75	TR, OS, PFS	rs11615	T: 0.240
Huang et al. (37)	China	Gastric	FOLFOX	89	OS, PFS	rs11615	T: 0.281
Liang et al. (38)	China	Colorectal	FOLFOX or XELOX	113	OS	rs11615	T: 0.323
Caucasians							
Le Morvan et al. (39)	France	Colorectal	FOLFOX or XELOX	59	TR, OS, PFS	rs13181	G: 0.381
Paré et al. (20)	Spain	Colorectal	FOLFOX	126	TR, OS, PFS	rs11615	T: 0.586
						rs13181	G: 0.384
Park et al. (40)	USA	Colorectal	FOLFOX	70	TR	rs13181	G: 0.421
Chua et al. (41)	Australia	Colorectal	FOLFOX	115	TR, OS, PFS	rs11615	T: 0.635
Spindler et al. (42)	Denmark	Colorectal	XELOX	66	TR, PFS ^b	rs11615	T: 0.652
Viguier et al. (43)	France	Colorectal	FOLFOX	61	TR	rs11615	T: 0.557
Ruzzo et al. (44)	Italy	Colorectal	FOLFOX	166	PFS	rs11615	T: 0.557
						rs13181	G: 0.443
Stoehlmacher et al. (45)	USA	Colorectal	FOLFOX	106	OS, PFS	rs11615	T: 0.505
						rs13181	G: 0.373
Martinez-Balibrea et al. (46)	Spain	Colorectal	FOLFOX or XELOX	96	PFS	rs11615	T: 0.615
						rs13181	G: 0.354
Etienne-Grimaldi et al. (47)	France	Colorectal	FOLFOX	117	TR, OS, PFS	rs11615	T: 0.538
						rs13181	G: 0.385
HapMap^c							
	China	(normal)		137		rs11615	T: 0.243
				136		rs13181	G: 0.095
	Europe	(normal)		113		rs11615	T: 0.642
				113		rs13181	G: 0.332

Abbreviation: TR, therapeutic response.

^aAllele frequencies are shown as the T allele of *ERCC1* rs11615 and the G allele of *ERCC2* rs13181.

^bPFS data were not available.

^cData from http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap3r3_B36/.

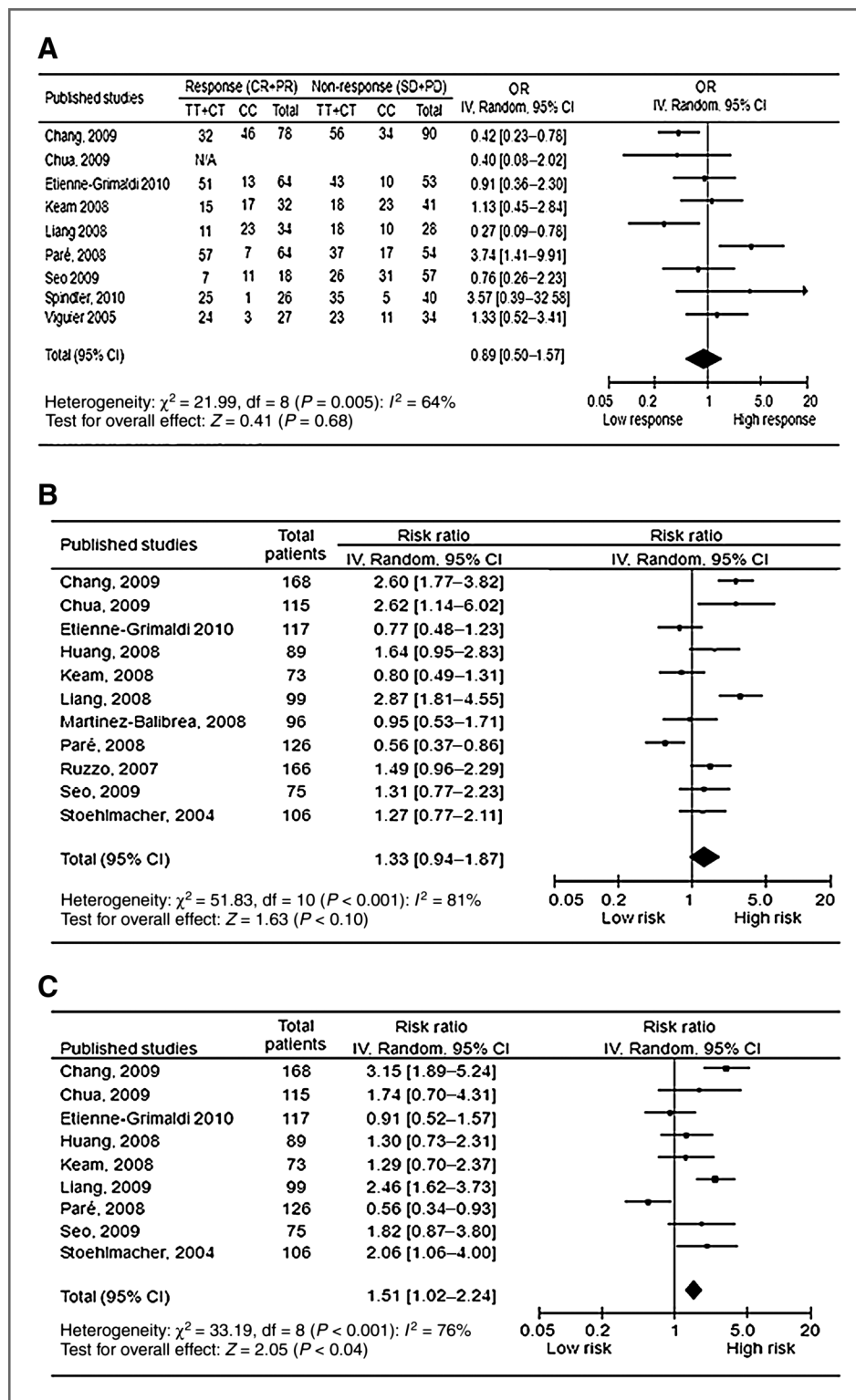


Figure 2. Forest plot of (A) objective response; (B) PFS; and (C) OS in gastric and colorectal cancer patients treated with oxaliplatin-based therapies by *ERCC1* rs11615C>T polymorphism (T/T + C/T vs. C/C, reference group = C/C).

1.33; 95% CI = 0.94–1.87; Fig. 2B), and the single study by Paré and colleagues (20) showed substantial influence over the pooled result, the exclusion of which elevated the HR significantly (HR = 1.46; 95% CI = 1.07–1.99). Although

stratified analysis by ethnicity showed a clinically substantial and statistically significant increase in the hazard of progression in Asian patients (HR = 1.69; 95% CI = 1.05–2.70), further comparison did not show significant

Table 2. Analysis of the association between *ERCC1* rs11615C>T and *ERCC2* rs13181T>G polymorphisms and objective response, PFS, and OS

	Objective response			PFS			OS				
	Study ^a (cases)	T/T + T/C vs. C/C		Study (cases)	T/T + T/C vs. C/C		Study (cases)	T/T + T/C vs. C/C			
		Phet ^b	Random effect		Phet ^b	Random effect		Phet ^b	Random effect		
<i>ERCC1</i> rs11615C>T											
All	9 (855)	0.81 (0.58-1.12)	0.89 (0.50-1.57)	0.005	1.33 (1.15-1.54)	1.33 (0.94-1.87)	11 (1,230)	1.33 (1.15-1.54)	1.53 (1.27-1.85)	1.51 (1.02-2.24)	<0.001
Asian	4 (378)	0.53 (0.35-0.81)	0.55 (0.31-0.98)	0.158	1.79 (1.45-2.21)	1.69 (1.05-2.70)	5 (504)	1.79 (1.45-2.21)	2.03 (1.60-2.59)	1.95 (1.37-2.78)	0.078
Caucasian	5 (477)	1.47 (0.89-2.43)	1.44 (0.68-3.02)	0.103	1.00 (0.81-1.23)	1.07 (0.72-1.59)	6 (726)	1.00 (0.81-1.23)	0.97 (0.72-1.32)	1.10 (0.60-2.03)	0.012
Colorectal only	7 (707)	0.77 (0.54-1.12)	0.88 (0.42-1.87)	0.002	1.38 (1.17-1.64)	1.39 (0.89-2.17)	8 (993)	1.38 (1.17-1.64)	1.58 (1.27-1.98)	1.55 (0.87-2.77)	<0.001
<i>ERCC2</i> rs13181T>G											
All	6 (625)	0.53 (0.37-0.78)	0.53 (0.36-0.78)	0.588	1.37 (1.15-1.63)	1.41 (1.06-1.89)	8 (931)	1.37 (1.15-1.63)	1.61 (1.29-2.00)	1.54 (0.96-2.50)	<0.001
Asian	2 (261)	0.56 (0.35-0.88)	0.56 (0.35-0.89)	0.368	1.33 (1.09-1.62)	1.41 (1.02-1.95)	2 (261)	1.33 (1.09-1.62)	1.42 (1.11-1.81)	1.42 (1.06-1.90)	0.236
Caucasian	4 (364)	0.52 (0.35-0.77)	0.52 (0.35-0.77)	0.472	1.42 (1.19-1.71)	1.50 (1.11-2.02)	6 (670)	1.42 (1.19-1.71)	1.70 (1.36-2.13)	1.77 (1.11-2.84)	0.002

^aStudy: the number of studies included in the analysis.^bPhet: *P* value of between-study heterogeneity.

difference in the estimates of effect between Asians and Caucasians ($P = 0.147$). When only colorectal cancer was included, the HR was similar to that of overall patients (HR = 1.39; 95% CI = 0.89–2.17; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Overall survival. Nine studies including 968 patients were eligible for the final analysis. There seemed a significant effect of *ERCC1* rs11615C>T polymorphism on OS in all patients (T/T + C/T vs. C/C: HR = 1.51; 95% CI = 1.02–2.24; Fig. 2C). Further analysis showed substantial influence from the single study of Chang and colleagues (21), the exclusion of which led to the loss of significance of the pooled result (HR = 1.36; 95% CI = 0.92–2.02). Stratified analysis indicated a more pronounced effect in Asian patients (HR = 2.03; 95% CI = 1.60–2.59) than in the Caucasian patients (HR = 1.10; 95% CI = 0.60–2.03) and a marginally significant difference existed in the estimates of effect between these two ethnicities ($P = 0.064$). When only colorectal cancer was included, the T allele was associated with a nonsignificant increased hazard of death (HR = 1.55; 95% CI = 0.87–2.77; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

ERCC2 rs13181T>G

Objective response. Six studies including 625 patients were eligible for the final analysis. The G allele was associated with a reduced objective response in all patients (G/G + G/T vs. T/T: OR = 0.53; 95% CI = 0.37–0.78; Fig. 3A), and no single study influenced the pooled result substantially. In stratified analyses (Table 2), the association remained significant in subgroups of Caucasians (OR = 0.56; 95% CI = 0.35–0.88) and colorectal cancer (OR = 0.52; 95% CI = 0.35–0.77). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Progression-free survival. Eight eligible studies of 931 patients were included in the final analysis, only 2 of which included Asians. Overall, there was a substantial effect of the G allele on progression hazard in all patients (G/G + G/T vs. T/T: HR = 1.41; 95% CI = 1.06–1.89; Fig. 3B and Table 2), and no single study influenced the pooled result substantially. In stratified analyses (Table 2), the significance remained in subgroups of Caucasians (HR = 1.41; 95% CI = 1.02–1.95) and colorectal cancer (HR = 1.50; 95% CI = 1.11–2.02). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Overall survival. Six studies including 669 patients were eligible for the final analysis; again, only two of which included Asians. The G allele was associated with a nonsignificant increase in the hazard of death in all patients (G/G + G/T vs. T/T: HR = 1.54; 95% CI = 0.96–2.50; Fig. 3C and Table 2), and the single study by Keam and colleagues (22) had a substantial influence over the pooled result, the exclusion of which elevated the HR significantly (HR = 1.77; 95% CI = 1.11–2.84). In stratified analyses, the significance remained in subgroups of Caucasians (HR = 1.42; 95% CI = 1.11–1.81), and

colorectal cancer (HR = 1.77; 95% CI = 1.11–2.84). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

Discussion

In this meta-analysis, we provided evidence of an association between *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs and clinical outcomes of Asian and Caucasian patients with gastric and colorectal cancer, respectively, who were treated by oxaliplatin-based chemotherapy.

Previous studies showed that clinical outcomes, measured as either tumor progression or survival, were better in patients susceptible to higher levels of platinum-induced DNA adducts (23, 24). Resistance to platinum may result from numerous mechanisms (25), among which NER is the predominant mechanism for moderate levels of platinum resistance seen clinically (26). There is evidence that cancer patients with congenital NER mutations are sensitive to platinum treatment and that hypersensitivity of testicular cancer to cisplatin is due to DNA repair deficiency (27, 28). *ERCC1* and *ERCC2* are two key rate-limiting enzymes in the multistep NER process. *ERCC1*, in collaboration with the XPF protein, is involved in DNA lesion recognition, whereas *ERCC2* is a subunit of human transcriptional initiation factor TFIIH with ATP-dependent helicase activity. Therefore, functional *ERCC1* and *ERCC2* SNPs may contribute directly to phenotypes of drug sensitivity by modifying functions of the related genes and reflect platinum sensitivity as an inborn trait.

Our meta-analysis used objective response, PFS, and OS as primary parameters to assess the influence of NER SNPs on clinical outcomes of oxaliplatin-based chemotherapy because these parameters are intrinsically correlated but not necessarily consistent with one another. Most often, a low objective response rate suggests tumor resistance to the chemotherapeutic regimen and a short PFS and OS is very likely the consequence. However, a high objective response rate may lead to an increased PFS and OS or no survival benefit at all (29), showing the necessity of including all 3 parameters to make a comprehensive assessment. In our meta-analysis, *ERCC1* rs11615 T allele was a biomarker of low objective response, a short PFS, and OS in Asian patients, whereas *ERCC2* rs13181 G allele showed significant or marginally significant association with low objective response, a short PFS, and OS in overall patients, Caucasians, and colorectal cancer subgroups. Although some single studies may have influenced the significance of the pooled results, the association tendency was obvious with or without these studies. The consistent changes of 3 parameters strongly suggested that *ERCC1* rs11615C>T and *ERCC2* rs13181T>G both had an effect on oxaliplatin-based chemotherapy and that objective response could be a useful surrogate of survival in oxaliplatin-treated gastric and colorectal cancer patients.

Our results could be reasonably explained by the biological significance of these 2 SNPs. The rs11615 T

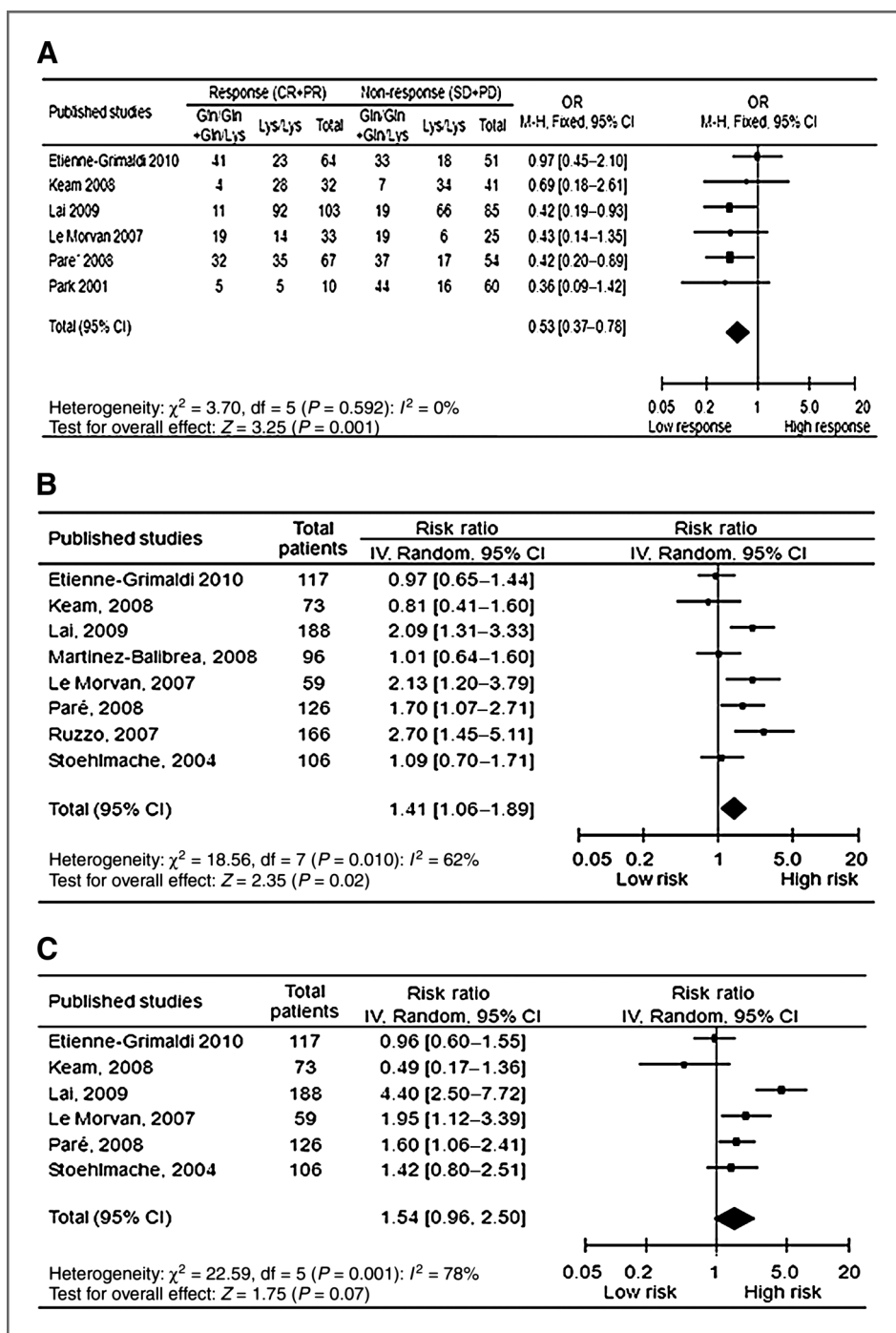


Figure 3. Forest plot of (A) objective response; (B) PFS; and (C) OS in gastric and colorectal cancer patients treated with oxaliplatin-based therapies by *ERCC2* rs13181T>G polymorphism (G/G + G/T vs. T/T, reference group = T/T).

allele of *ERCC1* polymorphism was found to be associated with high mRNA expression of the corresponding gene (30), whereas the rs13181 G allele of *ERCC2* polymorphism was found to be associated with a low number of X-ray-induced chromatid aberrations (8). Functional studies confirmed a substantial influence of the *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs on the phenotype of NER capacity (7, 31, 32), and possessing the TT genotype of *ERCC2* rs13181T>G SNP was associated with the risk of suboptimal DNA repair

up to 7-fold, compared with the GG/GT genotypes (8). Hence, patients carrying the *ERCC1* rs11615 T or *ERCC2* rs13181 G allele may have higher DNA repair capacity that could effectively reduce the anticancer effect of oxaliplatin, leading to poor prognosis of these patients.

Notably, there was an apparent ethnic discrepancy in the prognostic values between Asians and Caucasians and statistical test also confirmed the existence of ethnical difference in the estimates of effect for the *ERCC1* rs11615 T

allele. As shown in Table 1, there was a remarkably lower prevalence of *ERCC2* rs13181 G allele in Asians than in Caucasians, which might explain the lack of effect of *ERCC2* rs13181T>G SNP in Asian patients. However, it is interesting to find that there was no predictive value of *ERCC1* rs11615C>T SNP in Caucasians, even though the rs11615 T allele was much more common in Caucasians than in Asians. Although the underlying mechanisms are not clear, numerous factors, such as gene–gene interaction from different genetic background and gene–environment interaction from different lifestyles, may have played a role. Additional large studies are warranted to investigate these possibilities.

Despite our efforts to make an accurate and comprehensive analysis, limitations of our meta-analysis need to be addressed. First, some data were excluded from our analysis because of loss of contact (16) or missing data in the original study (33), which could cause some bias in our estimates but was unlikely to change our major conclusions, because Spindler and colleagues showed no association between *ERCC1* rs11615C>T polymorphism and PFS in Caucasians (33) and Liu and colleagues showed no association between *ERCC2* rs13181T>G polymorphism and OS in Asians (16), which were consistent with our findings. Second, most of the included studies were retrospective and differed significantly in study designs. In addition, the frequencies of *ERCC1* rs11615 T and *ERCC2* rs13181 G alleles were also substantially different among patient populations with different ethnicity. All these may have caused wide and significant heterogeneity between studies. Third, our analysis largely used unadjusted estimates, because not all published studies presented adjusted estimates or when they did, the estimates were not adjusted by the same potential confounders. However, when only those studies with the available adjusted estimates were used, the conclusions were not significantly changed (data not shown). Fourth, we were unable to analyze the association between *ERCC1* and *ERCC2* SNPs and platinum toxicities, because few studies provided this information or used different toxicity profiles. Finally, oxaliplatin is

not used as a single compound but in combination with 5-Fu in the regimen, and unfortunately, we were unable to investigate potential gene–gene interactions between NER variants and folate-metabolizing gene variants because of the limited publications available on this topic.

Overall, our meta-analysis showed that *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs might be useful prognostic factors for assessing clinical outcomes of oxaliplatin-based chemotherapies (FOLFOX or XELOX) in gastric and colorectal cancer. However, future prospective studies with large sample sizes and better study designs are required to confirm our findings.

Disclosure of Potential Conflicts of Interest

The authors have declared no conflicts of interest. The contents of the study are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Authors' Contributions

M. Yin, J. Yan, Q. Wei conceived the ideas, conducted literature search, and data collection; E. Martinez-Balibrea, F. Graziano, H.-J. Lenz, H.-J. Kim, J. Robert, S.-A. Im, W.-S. Wang, and M.-C. Etienne-Grimaldi provided the raw data of their original studies, and all authors contributed to the writing, revising, and approval for final submission.

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